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Chemistry at Cambridge Newsletter

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Going green and air-cooled computers
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The importance of **chemical safety**

Unnatural amino acids and protein modification

Jason Chin is looking at ways in which proteins can be altered to change their properties, which can create new therapeutics, and even give an insight into what's going on inside living cells

Photos: Nathan Pitt

Despite having chosen Oxford over Cambridge as an undergraduate because he wanted to focus solely on chemistry, during his time there Jason Chin found himself increasingly drawn to the interface between chemistry and biology, partly as a result of his final-year project with John Sutherland, now a colleague at the LMB.

'This was – as much research at Oxford was at that time – on the biosynthesis of cephalosporin and penicillin,' he says. 'It was my first exposure to molecular biology, and I've been hooked ever since.'

He was drawn to the US and Yale for a PhD because of the taught courses that are available in the first year there. He took all the biology courses and then, although his PhD with Alanna Schepartz, was in chemistry, he used a lot of biological methods such as phage display to help him develop high-affinity binders for protein and DNA targets.

A postdoc with Peter Schultz at the Scripps Institute in California pushed him towards the broad area he's been working on in his group at the LMB since he returned to the UK in 2003 – inserting novel types of amino acids into proteins to modify their function in a very specific way.

Proteins are, essentially, polymers that are made in the cell, with amino acids being strung together to make polypeptides. This is done by the ribosome, which is the cell's large molecular 'machine' that assembles the peptide bonds between the amino acid residues to build up the proteins.

'We are interested in synthesising new types of amino acids, and then engineering the cell to use them to make new proteins,' Jason says. 'Instead of building a protein where each monomer is one of just 20 possible amino acids, there are now additional choices that can be built into the polymer chain. These are encoded in the DNA, which provides all the information the ribosome needs to put the amino acids together in the right order. We can now encode the incorporation of these new kinds of building blocks into proteins and cells in a very specific way. It's a complete fusion of engineering biology, and synthetic chemistry to make the molecules that biology uses to construct the protein.'

Below: structure of the curcubiturils and the formation of a hydrogel, enabling the slow release of medications

One application these altered proteins might have is in the development of novel pharmaceuticals. Eight out of the current top 20 biggest selling drugs are proteins of one form or another, and very many others are under development. 'One of the way in which protein therapeutics can be improved is by adding components to the protein chain that will prevent them from being metabolised too quickly, for example,' he says.

'In fact, a biotech company is using early versions of this sort of technology that I developed during my postdoc at Scripps, and various molecules are already in clinical trials for conditions as diverse as multiple sclerosis, cancer and diabetes. By derivatising protein therapeutics in some way that stabilises them, perhaps the dose the patient needs to take will be lower, or they might even be made more efficacious.'

His group has also been developing methods for putting just one or two unnatural amino acids very precisely into a protein sequence. The ability to do this has real potential in providing a better understanding of how natural biology works. 'For example, if we label proteins with fluorophores, we can then look at what those proteins are doing inside the cell by light microscopy,' he says. 'The protein will glow inside the cell, so we can see where it goes.'

PROTEIN INTERACTIONS

Another project involves developing ways to figure out which proteins interact with each other. This is how a lot of biology is regulated, so being able to see the interactions will give a real insight into what is going on. 'We've created ways techniques to put photo-crosslinkers into proteins,' Jason explains. 'These are amino acids that, when you shine a light on them, become photoactivated to an excited state, so they form covalent bonds with other neighbouring proteins.

'We can then use analytical methods to see which proteins are now linked. This enables us to identify precisely what the labelled protein was interact-

ing with at the instant the light was shone on it. If we really want to understand how biology works at a molecular level, this is exactly the sort of fundamental question we have to ask – about which molecules are interacting with each other, and how.'

This work led on to a programme investigating ways to activate the function of enzyme proteins inside cells using pulses of light. 'We take the active site of the enzyme, and replace an amino acid there with another that bears a protecting group that can be removed by shining a light on it,' he says. 'So when we illuminate the cell, the enzyme immediately becomes active, enabling us to try and understand what happens when an enzyme is activated at a specific site within the cell. All of these techniques combine the ability to control the molecular properties of an individual amino acid using chemistry, and then to position it precisely within a protein using genetics and biology.'

CHEMICAL CHANGES

The study of post-translational modifications has become extremely important in recently years. While the gene codes for the proteins that are made by the ribosome, that's not the end of the story – enzymes act on some of the amino acid sidechains within that protein to introduce chemical changes, perhaps by phosphorylating, acetylating or methylating them. This regulates the activity and the function of what the protein does within the cell.

While mass spectrometry has been used to catalogue many of these modifications and what look like, it has been much more challenging to make the modified proteins synthetically, and understand exactly what the alterations do to the function of the proteins.

'Using our approaches to protein modification, we've developed techniques for installing these modifications without any need to know the identity of the natural enzyme that causes the modification,' he says. 'By recreating the post-translational modifications in the lab, it allows us to understand how they affect the structure and function of proteins and, again, lets us dig deeper insto how these modifications regulate biological function.'

Unusually, Jason's lab carries out experiments right through from chemistry to genetic manipulations to whole animal biology. 'We have a set of labs with chemistry space, molecular biology space, and space for doing cell biology and animal biology,' he says.

'The background of the people in the group is quite diverse – all the way from fly and worm geneticists to people whose PhD is in total synthesis. Postdocs will bring in their own particular expertise, but they are encouraged to work across these areas, and the lab is driven by an interest in asking and answering questions, rather than an overriding interest in any particular techniques. Everyone has to be able to explain not only why they find their individual questions interesting, but why in a broader sense they are interesting. It's a healthy reality check on the science we do, and its value to the wider society.'

One of the really interesting frontiers for chemistry in his lab, Jason believes, is the work on developing chemical reactions that take place in water inside living cells, and happen very rapidly without reacting with anything else in the biological system.

'We've put quite a bit of effort into developing unnatural amino acids that we can put into proteins and then label with, for example, fluorophores,' he says. 'And recently this field has started to move a lot more quickly because, until relatively recently, a lot of the reactions people were use were simply too slow. We have now been able to develop reactions that allow you to carry out chemical reactions inside living cells on specific proteins, and we're very excited about this.

'But at the other end of the spectrum, we've developed approaches that allow you to put new amino acids into proteins in specific tissues within whole animals. We think these types of approaches are going to be particularly useful in terms of studying the precise molecular mechanisms of how biology works in, say, the nervous system, in learning and memory.

'We'd really like to bring to some of these complicated areas the kind of precision that is more typically associated with molecular descriptions of processes. The goal here is to bridge this gap between really complicated phenomena, and a molecular level description of what is going on – and provide tools that will allow us to do this.'

SYNTHESIS WITH GENETICS

Another area in which he has had a long-term interest is the translation system itself. 'The ribosome is unrivalled in the way it builds polymers,' he says. 'It takes a nucleic acid template – DNA – and the genome gets copied to RNA. The ribosome then reads thousands and thousands of bases in triplets in the RNA, with each three successive bases coding for a specific amino acid, and decodes them one after another to build a really long polypeptide.

'This polymer has a defined sequence and composition, and is made with a really low error rate. So if you were able to reprogramme that system to make different types of polymers, the potential would be enormous. We're not just talking about being able to make modified, stabilised versions of existing protein therapeutics – we're talking about being able to explore the synthesis of new types of materials using genetics. These might be entirely new classes of therapeutic molecules, using the natural evolutionary processes that biology uses to make molecules functional from random sequences, but to redirect those processes to make new types of polymers. How can we co-opt biology to do our chemistry for us?'

Jason and his group squeeze into shot!

Jason Chin

CV

Born: London, where he grew up and went to school

Education: A chemistry degree at Oxford was followed by a PhD at Yale with Alanna Schepartz

Career: From Yale, he moved across the US to the Scripps Institute in San Diego and a postdoc with Peter Schultz. He moved back to the UK to start his own group the LMB in 2003, and was promoted to professor this year

Status: His wife Stacey works at the pharmaceutical company Medimmune; they have two children, William who's 6, and Rosalind, who's 3

Interests: Having fun with the family, particularly outdoor activities like walking and going to the park.

I don't remember reading anything about raining fire in the safety documentation

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